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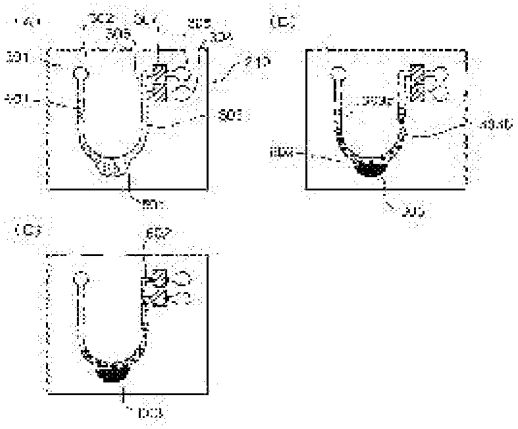
(54) BLOOD ANALYZER AND PLASMA SEPARATION METHOD

(57)Abstract:
PROBLEM TO BE SOLVED: To relax the load of a blood donor by effectively utilizing the total blood sample introduced into a passage to reduce the length of the passage and to miniaturize an automatic analyzer and by reducing the amount of collected blood, in an automatic analyzer for separating plasma in the passage by a centrifugal operation.
SOLUTION: A blood cell reservoir for depositing blood cells in the centrifugal direction in the centrifugal separation is disposed in the passage in the blood analyzer, and the the blood cells are accumulated there by the centrifugal separation, so that plasma fractions on the upstream and downstream sides of the U-shaped passage are continuously present without being separated by a blood cell fraction. A required quantity of the plasma can be introduced to an analysis means with a relatively small total quantity of blood. Since the total blood sample can effectively be used, this structure is suitable for reducing the length of the passage and for miniaturizing the analyzer. The plasma without being separated by the blood cell fraction can be moved by small suction negative pressure. Since pump ability required for sucking the plasma can be reduced, a peripheral device can be miniaturized and reduced in cost.



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* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1]
In hemanalysis equipment equipped with the passage which opens between a blood inlet and exhaust ports for free passage, and the plasma skimming means established in the middle of this passage :
Said passage is equipped with the upper section of said passage extended in the centrifugal-force pressurization direction, and the downstream extended to centrifugal-force pressurization hard flow.;
It is hemanalysis equipment which these passage upstream section and a downstream do, and said plasma skimming means is equipped with the corpuscle fractionation hold section which it is located in the centrifugal-force pressurization direction side, and corpuscle fractionation is settled, and is held, and is characterized by constituting the upper section and the downstream of said passage so that it may be mutually open for free passage in the upper part of the corpuscle fractionation hold section, ****(ing) in the corpuscle fractionation hold section.
[Claim 2]
Said a part of passage [at least] is hemanalysis equipment of claim 1 characterized by being U character mold passage and this U character mold passage bottom being said corpuscle fractionation hold section.
[Claim 3]
Said a part of passage [at least] consists of U character mold passage, and this U character mold passage bottom is said corpuscle fractionation hold section,
Hemanalysis equipment of claim 1 with which the volume of said corpuscle fractionation hold section located in the centrifugal-force pressurization direction from the lowermost up wall in U character mold passage is characterized by being size rather than the amount of corpuscle fractionation in the blood introduced into said passage.
[Claim 4]
Hemanalysis equipment of claim 1 characterized by having said plasma skimming means and an analysis means to perform component analysis of plasma between said exhaust ports.
[Claim 5]
Hemanalysis equipment of claim 1 characterized by enabling installation of a blood collecting needle in said blood inlet.
[Claim 6]

The plasma skimming approach which consists of the following steps :
(1) Passage equipped with the upper section which is the passage which opens between a blood inlet and exhaust ports for free passage, and is extended in the centrifugal-force pressurization direction from a blood inlet, and the downstream which is in this lower stream of a river, and is extended to centrifugal-force pressurization hard flow;
Having the corpuscle fractionation hold section which the passage upstream section and a downstream do, it is located in the centrifugal-force pressurization direction side, and a corpuscle component is settled, and is held, they prepare chip-like hemanalysis equipment equipped with the plasma skimming means constituted so that it may be mutually open for free passage in the upper part of the corpuscle fractionation hold section, ****(ing) the upper section and the downstream of said passage in the corpuscle fractionation hold section.;
(2) Introduce a whole blood sample into said passage from said blood inlet.;
(3) Make the plasma divided into the upper section and the downstream of said passage as centrifugal supernatant liquid exist continuously mutually, while settling the corpuscle component in a blood sample in said corpuscle fractionation hold section by carrying out centrifugal [of the hemanalysis equipment] so that said corpuscle fractionation hold section may serve as the centrifugal-force pressurization direction, touching the corpuscle fractionation of said corpuscle fractionation hold circles.
[Claim 7]
Said hemanalysis equipment is equipped with said plasma skimming means and an analysis means to perform component analysis in plasma between said exhaust ports,
The plasma skimming approach according to claim 6 characterized by leading the plasma which exists continuously after said step (3) at the upper section and the downstream of said passage to said analysis means.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]
This invention relates to the chip-like hemanalysis equipment constituted by the micro slot passage produced to insulating material substrates, such as a quartz plate and a giant-molecule resin plate. Especially, the blood of a minute amount (below several microL) is introduced into the slot passage on the chip concerned, and centrifugal separation is performed, and after separating into corpuscle fractionation and a plasma component, it is related with the slot passage structure of the plasma skimming approach for utilizing effectively the plasma component concerned at the time of measuring the various chemical concentration in a plasma component, and such chip-like hemanalysis equipment.
[0002]
[Description of the Prior Art]

The conventional medical checkup and the diagnosis of an illness condition extracted a lot of several cc blood from the patient, and have been performed from the measured value obtained with large-scale automatic hemanalysis equipment to the analysis. Usually, such an automatic analyzer was installed in medical institutions, such as a hospital, the scale was large and the actuation was what is restricted to what has special rating.

[0003]

However, the ultra-fine processing technology used for semiconductor device production which progressed to the degree of pole is applied, analysis apparatus, such as various sensors, are arranged on the chip of several cm around at most from several mm, body fluid, such as a test subject's blood, is led there, and development of the new device which can grasp a test subject's health condition in an instant, and the tendency of the utilization have been increasing in recent years. Compression of the health insurance benefits an increment of which is enhanced can be aimed at by making the health care of old every day possible at home in this **** aging society with such the cheap advent of a device etc. Moreover, if the existence of a test subject's infectious diseases (hepatitis, acquired immunodeficiency, etc.) can be quickly judged using this device in the site of emergency medical service, since various social effectiveness is expected, that suitable correspondence can be performed etc. will be the technical field which is attracting attention very much. Thus, instead of the conventional automatic analyzer, the small simple hemanalysis approach and hemanalysis equipment which aimed at carrying out the hemanalysis by one's hand at each home are developed. (for example, patent reference 1 reference) .

[0004]

[Patent reference 1]

JP,2001-258868,A

[0005]

Drawing 1 shows an example of the micro-module-ized hemanalysis equipment which was indicated by the patent reference 1. A sign 101 is the bottom substrate of hemanalysis equipment, and the detailed slot passage (micro capillary) 102 formed by etching on the bottom substrate is formed. On this bottom substrate 102, the top substrate (un-illustrating) of abbreviation same size was stretched, and the slot passage 102 is sealed from the outside.

[0006]

It applies to the lowest style section from the maximum upstream section, and the blood extraction means 103, the plasma skimming means 104, the analysis means 105, and the migration means 106 are formed in passage 102 one by one. Blood collecting needle 103a in the air is attached, the inside of the body is stabbed with this needle 103a, and it considers as the intake of the blood into a substrate at the foremost blood extraction means 103 in passage. The separation means 104 incurvated the middle of passage 102, and consists of a micro capillary of a U character mold. After leading the extracted blood to this U character type of micro capillary, by applying acceleration in the fixed direction for this substrate with a centrifugal separation vessel, a corpuscle component is settled at the U character section bottom, and plasma is separated as supernatant liquid. The analysis means 105 is a sensor for measuring each concentration, such as the pH value in blood, oxygen, a carbon dioxide, sodium, a potassium, calcium, a glucose, and a lactic acid.

[0007]

A migration means 106 by which it is located in the passage lowest style section moves blood by the electroendosmose style in a micro capillary, and consists of a passage part 109 which connects the meantime with electrodes 107 and 108. The buffer solution beforehand filled in passage by the electroendosmose style which carries out electrical-potential-difference impression, and which is produced in inter-electrode [this] is moved to the passage downstream, and blood is taken in in a substrate from the extraction means 103 of the passage 102 foremost part with the suction force to produce. Moreover, the plasma obtained according to centrifugal separation is led to the analysis means 105.

[0008]

110 is an output means for taking out information from an analysis means, and consists of electrodes etc. 111 is a control means for controlling the above extraction means, a plasma

skimming means, an analysis means, a migration means, and an output means if needed.
[0009]
It is separated into plasma and a corpuscle component by the separation means 104, and the blood extracted from the extraction means 103 leads this plasma component to the analysis means 105, and measures each concentration, such as the pH value in plasma, oxygen, a carbon dioxide, sodium, a potassium, calcium, a glucose, and a lactic acid, there. A migration means 106 to have pump capacity, such as what used phenomena, such as electrophoresis and electroendosmose, performs migration of the blood between each means. In addition, in drawing 1 , the down-stream region of passage 102 branches to five, and the analysis means 105 and the migration means 106 are formed in this each.
[0010]
Although glass ingredients, such as a quartz, were used for the substrate of such hemanalysis equipment in many cases, a resin material is increasingly used as what is suitable holding down costs and manufacturing equipment in large quantities again.
[0011]
[Problem(s) to be Solved by the Invention]
In the case of the conventional hemanalysis equipment shown in drawing 1 , blood is extracted with the extraction means 103, the separation means 104 separates into plasma and a corpuscle component, this plasma component is led to an analysis means, and various component analysis in plasma is performed. However, in a separation means, if centrifugal separation separates blood into plasma and a corpuscle component, the corpuscle fractionation which precipitated at the U character passage bottom will take up passage, and the plasma which is supernatant liquid will be divided by upstream 102a and downstream 102b of U character passage. For this reason, only the plasma of the downstream could be led to the analysis means, but the plasma component of the upstream had the problem that it could not use.
[0012]
This situation is briefly explained using drawing 2 . Drawing 2 shows the situation of production of conventional hemanalysis equipment. The bottom substrate 301 and upper substrate 301A which consisted of two substrates, for example, an ingredient like resin, first as shown in this drawing (A) are prepared, and width of face of about 100 microns and the slot passage 303 with a depth of about 100 microns are formed by approaches, such as molding, on one bottom substrate 301. U character mold passage is included so that a part of this slot passage 303 may be illustrated. On upper substrate 301A, in order to draw the input-side through hole 302 for introducing inspected blood, and blood in passage, an analysis means 306,307 to detect an item different, respectively in the output side through hole 304,305 for connecting an external pump and plasma is constituted. Both the substrates 301,301A2 of each other are joined with thermocompression bonding, adhesives, adhesive tape, etc., and hemanalysis equipment 200 is produced (this drawing (B)).
[0013]
Drawing 3 is the mimetic diagram of the hemanalysis equipment produced in this way, and shows signs that introduce Homo sapiens whole blood into the passage of hemanalysis equipment, and it carries out centrifugal separation. 1micro about L blood is dripped to the input-side through hole (blood inlet) 302 of the hemanalysis equipment shown in drawing 3 (A) (this drawing (B)), and whole blood 308 is led to passage 303 with a pump from the output side through holes (exhaust port) 304 and 305 (this drawing (C)). Next, hemanalysis equipment 200 is rotated and centrifugal separation is performed so that the force may act in the direction of U character passage (the direction of an arrow head in this drawing (C)). Then, as shown in this drawing (D), whole blood is divided into plasma fractionation 309 and 310 and the U character passage lower part by the corpuscle fractionation 311 at the both sides of the U character passage 303. A pump etc. is connected to the output side through holes 304 and 305 after that, the downstream plasma fractionation 310 is led to the analysis means 306 and 307 (this drawing (E)), and detection and density measurement of each inspected chemical are performed there.
[0014]
However, in the case of such U character passage, the upstream plasma fractionation 309 shown

in this drawing (D) has passage taken up by the corpuscle fractionation 311, and cannot be used, being able to lead to an analysis means. It means that this is making blood volume required for inspection increase superfluously, and if the plasma fractionation of such the upstream can also be led to an analysis means and can be used, blood volume required for inspection can decrease even in abbreviation one half simply. This shortens the overall length of passage, as a result enables the further miniaturization of the whole hemanalysis equipment.
[0015]
Moreover, with the conventional hemanalysis equipment of drawing 1 -3, as shown in drawing 3 (E), in case the downstream plasma component 310 is led to the analysis means 306 and 307 after the centrifugal separation of whole blood, the corpuscle fractionation 311 and the upstream plasma component 309 must also be moved to coincidence. At this time, since the corpuscle fractionation 311 is sticking to the wall of passage 303, in order to move these with a pump etc., it had the problem that the need of the bigger suction-force pump force than the time of drawing whole blood before centrifugal in passage was carried out.
[0016]
[The technical problem which is going to solve a technical problem]
If the bypass passage 401 is newly formed between the upstream of U character passage, and the downstream as a means to solve the above technical problems as shown in drawing 4 , upstream plasma can be led to the downstream after centrifugal separation. However, it becomes large-scale equipment and is not realistic, if it is necessary to shut this bypass passage, valves 402 and 403 must newly be installed in the entrance of this bypass passage 401 and control of this is included until centrifugal separation is completed for that purpose.
[0017]
Then, the artificers of this invention tried to conquer the technical problem of equipment conventionally only by amelioration of some passage configuration by using this conversely paying attention to the corpuscle component after centrifugal separation sticking to the wall of passage. That is, passage of a part covered with a corpuscle component when a corpuscle component and a plasma component dissociate according to centrifugal separation was made thicker than other it, and the corpuscle component was accumulated there, and it is made for the plasma component of the upstream and the downstream to be continuously connected with plasma through the part on which the corpuscle of the reservoir part has not collected. If plasma is drawn in an analysis means with a pump etc. after doing in this way, since the plasma of the upstream and the downstream is connected continuously, so big the pump force cannot be needed and all the separated plasma components can be led to an analysis means.
[0018]
That is, this invention is an automatic analyzer which performs plasma skimming in passage by centrifugal actuation, it aims at a deployment of the whole blood sample introduced in passage, is suitable for shortening of passage length, and the miniaturization of equipment, and sets it as the 1st purpose to offer the hemanalysis equipment which can mitigate the burden of a collected blood person by decreasing the amount of blood collecting further.
[0019]
Moreover, in case the automatic analyzer which performs plasma skimming in passage by centrifugal actuation is used for this invention, it aims at offering the plasma skimming approach that a deployment of the whole blood sample introduced in passage can be aimed at.
[0020]
[Elements of the Invention]
the passage where the 1st purpose opens between a blood inlet and exhaust ports for free passage according to this invention, and this passage -- on the way -- hemanalysis equipment equipped with the plasma skimming means boiled and established -- setting -- : -- said passage Have the upper section of said passage extended in the centrifugal-force pressurization direction, and the downstream extended to centrifugal-force pressurization hard flow, and, as for the; aforementioned plasma skimming means, these passage upstream section and a downstream do. It has the corpuscle fractionation hold section which it is located in the centrifugal-force pressurization direction side, and corpuscle fractionation is settled, and is held, and they are

attained more by the hemanalysis equipment characterized by being constituted so that it may be mutually open for free passage in the upper part of the corpuscle fractionation hold section, ****(ing) the upper section and the downstream of said passage in the corpuscle fractionation hold section.

[0021]

For example, U character mold passage, then this U character mold passage bottom (part which requires G of a centrifugal force) can be made into the corpuscle fractionation hold section for a part of passage. Rather than the amount of corpuscle fractionation in the blood with which the volume of the corpuscle fractionation hold section located in the centrifugal-force pressurization direction from the lowermost up wall in U character mold passage that this corpuscle fractionation hold section should just be the space projected in the lower part (the centrifugal G load direction) from the bottom of U character mold passage is introduced into said passage, if it is size, the upper part of the corpuscle fractionation hold section can open the supernatant liquid plasma of the upper section and a downstream for free passage.

[0022]

A plasma skimming means and an analysis means to perform component analysis of plasma between exhaust ports may be established. Moreover, installation of a blood collecting needle being possible, then the whole blood which collected blood from the blood collecting needle can be introduced into a blood inlet in direct passage.

[0023]

The 2nd purpose of this invention is the plasma skimming approach which consists of the following steps. :

(1) Passage equipped with the upper section which is the passage which opens between a blood inlet and exhaust ports for free passage, and is extended in the centrifugal-force pressurization direction from a blood inlet, and the downstream which is in this lower stream of a river, and is extended to centrifugal-force pressurization hard flow;

Having the corpuscle fractionation hold section which the passage upstream section and a downstream do, it is located in the centrifugal-force pressurization direction side, and a corpuscle component is settled, and is held, they prepare chip-like hemanalysis equipment equipped with the plasma skimming means constituted so that it may be mutually open for free passage in the upper part of the corpuscle fractionation hold section, ****(ing) the upper section and the downstream of said passage in the corpuscle fractionation hold section.;

(2) Introduce a whole blood sample into said passage from said blood inlet.;

(3) While settling the corpuscle component in a blood sample in said corpuscle fractionation hold section by carrying out centrifugal [of the hemanalysis equipment] so that said corpuscle fractionation hold section may serve as the centrifugal-force pressurization direction, it can attain "Making it exist continuously mutually and boil the plasma divided into the upper section and the downstream of said passage as centrifugal supernatant liquid, touching the corpuscle fractionation of said corpuscle fractionation hold circles."

[0024]

When it has the plasma skimming means of hemanalysis equipment, and an analysis means to perform component analysis in plasma between exhaust ports, the plasma which exists continuously after a step (3) at the upper section and the downstream of passage can be led to an analysis means.

[0025]

[Embodiment of the Invention]

Drawing 5 shows one embodiment of the hemanalysis equipment which has the passage based on this invention. Although this hemanalysis equipment 210 is the fundamentally almost same configuration as the equipment 200 shown in drawing 3 , the passage 303 of the hit where gravitational acceleration is most impressed at the time of the lowermost centrifugal separation in U character passage is narrowed, and it differs in that there is corpuscle reservoir (corpuscle fractionation hold section) 501 made large. Since the same sign is given to the same component, explanation is not repeated.

[0026]

The situation of actuation of this hemanalysis equipment is explained below. As shown in drawing 6 (A), after introducing whole blood into hemanalysis equipment, the hemanalysis equipment 210 concerned is set in a centrifugal separator as shown in drawing 7 , and centrifugal separation of whole blood is performed. As there is corpuscle reservoir 501 on hemanalysis equipment in the rotational centrifugal direction at this time, hemanalysis equipment 210 is installed, and corpuscle fractionation precipitates by centrifugal to this corpuscle reservoir 501. In addition, for 701, as for a shaft and 703, a motor and 702 are [a chip support plate and 706] balancer chips.
[0027]
The situation in the passage of the hemanalysis equipment 210 after centrifugal actuation is shown in drawing 6 (B). The corpuscle fractionation 603 carries out centrifugation to the corpuscle reservoir 501 lower part, and the plasma component 602 is divided into the passage 303 of the upper part as supernatant liquid. At this time, existing continuously is important, without unlike the case (referring to drawing 3) of conventional hemanalysis equipment, plasma fractionation being missing from downstream 303b from upper section 303a in U character passage, and being divided by the corpuscle fractionation 603.
[0028]
It is made for that for the capacity of the corpuscle reservoir (corpuscle component hold section) 501 caudad located from the wall upper limit location A in the bottom of passage 303 so that it may illustrate to drawing 5 to serve as size from the amount of corpuscle components in the whole blood introduced into passage 303. Since a human blunder crit value is usually 50% or less, as for the capacity of the corpuscle reservoir (corpuscle component hold section) 501, it is desirable to carry out to 1/2 or more [of the amount of blood collecting]. The capacity of a corpuscle reservoir can also take into consideration and determine the passage length and the cross section of U character passage. In addition, a blunder crit value is high, and when fractionation of the corpuscle is carried out exceeding the corpuscle reservoir upper limit A, it can be coped with by reducing the amount of blood collecting.
[0029]
An external suction pump is connected to the service entrances (exhaust port) 304 and 305 arranged at the passage 303 lowest style section after centrifugal separation, and plasma fractionation 602 is drawn in the analysis means 306 and 307. Since the plasma fractionation 602 of downstream 303b of U character passage and upper section 303a is not interrupted by the corpuscle fractionation 603, all the separated plasma fractionation can be led to the analysis means 306,307 (drawing 6 (C)).
[0030]
Corpuscle fractionation has fixed by centrifugal load to the wall of the corpuscle reservoir 501 lower part. Therefore, in case suction migration of the plasma fractionation is carried out at an analysis means, corpuscle fractionation does not move. Suction migration of plasma can be performed only by migration of the plasma fractionation which is an acidity-or-alkalinity component, and the big pump force is not necessary like [in the former which also had to move corpuscle fractionation collectively].
[0031]
Thus, if it can exist continuously, without arranging the corpuscle reservoir to which a corpuscle precipitates in the centrifugal direction at the time of centrifugal separation to the passage in hemanalysis equipment, making a corpuscle then, accumulate according to centrifugal separation in it, and the upstream of U character passage and the plasma fractionation of the downstream being divided by corpuscle fractionation, the pump force which can draw all the separated plasma fractionation in an analysis means, and is needed for drawing in at that time will be low, and will end. Such a dimension of a corpuscle reservoir can be determined by taking into consideration that the 40 to 50% (volume) is a corpuscle component from the total blood volume which performs a U character passage dimension and centrifugal separation.
[0032]
In addition, in this embodiment, although installation of blood and suction of plasma fractionation were performed using the external pump, the migration means which used the electroendosmose style like the conventional equipment of drawing 1 R> 1 may be established between an analysis

means and a service entrance (exhaust port). In this case, an exhaust port 304,305 turns into an exhaust port of the buffer solution with which it filled up in passage.
[0033]
[The 1st example]
The hemanalysis equipment shown in drawing 5 was produced, the blood sample was introduced in hemanalysis equipment, centrifugal separation was performed, and plasma fractionation was attracted after that. However, since it was easy, the analysis means in hemanalysis equipment was set to one (refer to drawing 8). Hemanalysis equipment prepared two polyethylene terephthalate (PET) substrates of 0.5mm thickness, passage 303 was formed by molding on one substrate, and made what applied the hydrogen ion induction film on another substrate on the blood inlet 302, the blood service entrance (exhaust port) 801, and the electrode formed with carbon paste the analysis means 802, and has produced and arranged it. The outline of the dimension of the passage 303 formed on it is indicated to be hemanalysis equipment 210 to drawing 8 . In addition, all the depth of passage is 100 micrometers.
[0034]
The whole blood of the Homo sapiens of 1microL was introduced from the blood inlet 302 of this hemanalysis equipment 210. The suction force of the electromagnetic pump attached in the exhaust port 801 was used for installation of blood. The suction negative pressure at that time was −7kPa from atmospheric pressure. After blood installation, it carried out centrifugal [of the hemanalysis equipment] with the centrifuge as shown in drawing 7 (10000rpm, 2250 G or 1 minute). As the inside of the hemanalysis equipment passage after centrifugal was shown in drawing 6 (B), the corpuscle fractionation 603 precipitated in the corpuscle reservoir 501 lower part, and it dissociated so that a plasma component might exist continuously, without insulating plasma components by the corpuscle component in the U character passage of the corpuscle reservoir upper part and upstream, and a lower stream of a river. The electromagnetic pump was connected to the service entrance 304,305 which is in an analysis means downstream next, and the plasma component concerned was led to the analysis means. At this time, the corpuscle component did not move but only the plasma component moved it. When the hydrogen ion concentration in plasma was investigated here, pH 7.4 were shown and it was almost the same as a healthy person's plasma pH value. Moreover, plasma ********** was able to be drawn more satisfactory than the same atmospheric pressure as whole blood ********** at −7kPa.
[0035]
Moreover, the hemanalysis equipment of drawing 8 was converted and the trial with the same said of the case where the blood collecting needle of hollow with an outer diameter [of 100 micrometers] and a bore of 50 micrometers is attached in the blood inlet 302 was performed. The puncture of the blood collecting needle on hemanalysis equipment is first carried out to the human forearm section, the blood of about 1microL is extracted, and it leads on the hemanalysis equipment concerned. After that, centrifugal separation separated into plasma and corpuscle fractionation like the procedure described in the top, and only plasma was led to the analysis means. When the hydrogen ion concentration of plasma was investigated here, pH 7.4 were shown like the upper case and it was almost the same as the value of a healthy person's plasma.

[0036]
[Comparative Example(s)]
Drawing in for the plasma by drawing in of whole blood and centrifugal separation, corpuscle segregation, and the analysis means of a plasma component was similarly performed using the conventional hemanalysis equipment shown in drawing 3 . Width of face of the U character passage at this time was set to 500 micrometers, and the depth was set to 100 micrometers. Moreover, also in this case, the analysis means was set to one and what applied the hydrogen ion induction film on the electrode formed with carbon paste was used. The whole blood of the Homo sapiens of 1microL was introduced from the blood inlet 204 of such hemanalysis equipment. The suction negative pressure at that time was −7kPa from atmospheric pressure using the electromagnetic pump attached in installation of blood at the exhaust port 205.
[0037]

As it is shown in drawing 3 (C), after introducing blood in hemanalysis equipment, hemanalysis equipment was installed in the centrifugal separation machine as shown in drawing 7 , and centrifugal separation was performed (10000 rpm, 2250 G or 1 minute). As shown in drawing 3 (D), the plasma component 309,310 and the corpuscle component 311 were separated within the single U tube by centrifugal. Unlike the case of the hemanalysis equipment which has a corpuscle reservoir in the middle of passage as showed the description at this time to drawing 5 , the plasma component 309,310 of the upstream of single U character passage and the downstream was insulated by the corpuscle fractionation 311.

[0038]

The electromagnetic pump was connected to the service entrance 304,305 which is in an analysis means downstream next, and the plasma component 310 of the downstream of single U character passage was led to the analysis means 306,307. Plasma was not able to be drawn for the suction negative pressure at this time as the same −7kPa as the 1st example. Suction negative pressure is raised gradually and the plasma 310 of the passage downstream began to move in the place which reached −38kPa from atmospheric pressure. Moreover, the corpuscle component and upstream plasma component of the U character passage lower part also moved to coincidence with this migration. As compared with plasma ********** in the case of the 1st example, bigger plasma ********** was required of this example of a comparison. Thereby, the effectiveness of this invention became clearer.

[0039]

It is considered to be for having to draw a plasma component with a component in the corpuscle fractionation which has adhered to the wall of passage according to centrifugal separation that excessive draw and ** is such needed. In the case of single U character hemanalysis equipment still like drawing 3 , although it draws and plasma is drawn by **, the excessive plasma which can actually be drawn in an analysis means is only the plasma component divided into the downstream, and the plasma of the upstream closed with corpuscle fractionation cannot be drawn in an analysis means. Only the abbreviation one half of the plasma separated in conventional hemanalysis equipment can be led to an analysis means. On the other hand, in the case of the hemanalysis equipment which has a corpuscle reservoir of this invention shown in drawing 5 , all the separated plasma can be led to an analysis means. Therefore, when leading the plasma of tales doses to an analysis means, there is an advantage that the blood volume introduced in hemanalysis equipment is better than the case where the direction in the case of this invention is the former, in abbreviation one half.

[0040]

[The 2nd example]

The hemanalysis equipment 220 which has corpuscle reservoir 501A as shown in drawing 9 (A) was produced, blood was introduced in the hemanalysis equipment concerned, centrifugal separation was performed, and plasma fractionation 602 was drawn after that. In addition, the dimension of the hemanalysis equipment concerned and a passage configuration is mostly similar to the dimension shown in drawing 8 . The difference between that of this hemanalysis equipment and the hemanalysis equipment of drawing 8 is just going to be small as compared with the case of the hemanalysis equipment which the area of the interface of the separated plasma 602 and the corpuscle fractionation 603 showed by drawing 8 , when blood is introduced on hemanalysis equipment and centrifugal separation is performed, as shown in drawing 9 (B). The drawing-in force impressed to corpuscle fractionation at the time of plasma suction becomes small by this, it can prevent a corpuscle part tableau side being disturbed and mixing in plasma, and the thing of plasma for which all are mostly moved to an analysis means is ensured.

[0041]

When the whole blood of the Homo sapiens of 1microL was actually introduced from the blood inlet and centrifugal separation was performed, as shown in drawing 9 (B), the corpuscle and the plasma component were separated. Moreover, the pump was connected to the service entrance 801 after that, and when lengthened by the pressure of −7kPa from atmospheric pressure, only the plasma component 602 was able to be drawn in the analysis means 802 side. The corpuscle component which is in a corpuscle reservoir at this time did not move, but had stopped at the

corpuscle reservoir as it is.
[0042]
[The 3rd example]
As shown in drawing 10 (A), the hemanalysis equipment 230 which made large the depth of the U character passage 303 lower part, and set this to corpuscle reservoir 501B was produced, and installation of blood, plasma corpuscle segregation, and plasma component drawing in were tried like the 1st and 2 example. Consequently, only plasma fractionation 602 was able to be drawn without having separated plasma 602 and the corpuscle fractionation 603, as shown in drawing 10 R> 0 (B), and disturbing the corpuscle fractionation 603 according to the centrifugal separation after blood installation, and it was able to lead to the analysis means 802. When centrifugal separates into plasma and corpuscle fractionation from this example, it turns out that especially the thing existed continuously, without plasma fractionation being divided by corpuscle fractionation is important. This is the same also in the hemanalysis equipment which has the corpuscle reservoir shown in the 1st and 2 example in the middle of passage.
[0043]
[The 4th example]
The hemanalysis equipment which enlarged the depth and the passage depth of the U character passage 303 lower part was produced. That is, the hemanalysis equipment 240 which set to 300 micrometers deeper than a depth of 100 micrometers of other passage parts the depth of the slash section 1101 of the U character passage 303 lower part shown in drawing 11 (A) was produced. Installation of blood, plasma skimming, and plasma component drawing in were tried like the 3rd example. According to centrifugal separation, as shown in drawing 11 (B), it separated into plasma 602 and the corpuscle fractionation 603, and the corpuscle fractionation 603 was able to draw only plasma fractionation 602, without making it move, and was able to lead it to the analysis means 802.
[0044]
What should be observed here has the deep depth of the U character passage lower part 1101 of drawing 11 (A), and since it becomes large 3 times as compared with it of the hemanalysis equipment of drawing 10 , a corpuscle component accumulates the volume of this part here. Therefore, when the case of the 3rd example and the blood of tales doses are introduced on hemanalysis equipment and centrifugal separation is carried out, the configuration area of corpuscle fractionation 603 ** seen from the drawing 11 top face becomes [a plasma component] smaller [the ratio to the area to occupy] than the case of drawing 10 . Therefore, since the width of face which the plasma component in the U character passage lower part constitutes becomes large as compared with drawing 10 (B), in plasma component drawing in after this corpuscle and plasma segregation, the plasma component concerned can be drawn by the lower drawing-in pressure.
[0045]
[The 5th example]
Single U character passage hemanalysis equipment as shown in drawing 12 (A) was produced, and installation of blood, plasma corpuscle segregation, and plasma component drawing in were tried like the old example. At this time, the width of face and the depth of passage were determined from the amount (amount of needed plasma) of the blood to introduce. That is, it was made for a plasma component to exist continuously like drawing 12 (B) after centrifugal separation, without being divided by corpuscle fractionation on passage. The hemanalysis equipment 250 which has the single U character passage 303 with a passage depth of 100 micrometers with a dimension as actually shown in drawing 12 (C) was produced, the blood of 0.1microL was introduced on this hemanalysis equipment, and centrifugal separation was performed. Consequently, only all the plasma fractionation that separated into plasma fractionation 602 and the corpuscle fractionation 603 as shown in drawing 12 (B), and was separated after that was able to be led to the analysis means 802. Thus, if passage is designed so that the blood volume introduced from needed plasma volume may be estimated and a plasma component may not be divided by corpuscle fractionation on passage after centrifugal separation, a corpuscle reservoir as shown in drawing 5 is not necessarily required. The U

character passage bottom prepared based on the passage design will constitute a corpuscle reservoir (corpuscle fractionation hold section).
[0046]
[Effect of the Invention]
As mentioned above, the hemanalysis equipment of this invention prepares the corpuscle fractionation hold section which the centrifugal-force pressurization direction is located in a part of passage which introduces blood, and collects corpuscle fractionation in equipment, and the passage of the upstream of the hold section and the downstream opened it for free passage. Thereby, the plasma fractionation of the passage upstream section and a downstream can exist continuously, without being divided by the corpuscle fractionation after centrifugal separation. therefore, the case of the conventional passage configuration -- comparing -- smaller total blood volume -- it is the blood sample of a half amount simply, and the plasma of an initial complement can be led to an analysis means. Since a deployment of a whole blood sample can be aimed at, it is suitable for shortening of passage length, and the miniaturization of equipment. The burden of a collected blood person is mitigable by furthermore decreasing the amount of blood collecting.
[0047]
Moreover, since the separated plasma fractionation is not divided by corpuscle fractionation, it can be made to move with smaller suction negative pressure. Since pump capacity which plasma drawing in takes can be made small, the miniaturization of a peripheral device and a cost cut can be aimed at.
[Brief Description of the Drawings]
[Drawing 1] It is the explanatory view of conventional chip-like hemanalysis equipment.
[Drawing 2] It is the explanatory view of the process of chip-like hemanalysis equipment production.
[Drawing 3] It is drawing showing signs that introduce whole blood on hemanalysis equipment and centrifugal separation separates into a component at plasma and corpuscle fractionation.
[Drawing 4] It is drawing showing the example of modification of the configuration of conventional hemanalysis equipment.
[Drawing 5] It is the conceptual mimetic diagram of one embodiment of the hemanalysis equipment of this invention.
[Drawing 6] It is drawing explaining each process which introduces blood into the hemanalysis equipment of drawing 5 , separates into plasma and corpuscle fractionation, and leads plasma fractionation to an analysis means after that.
[Drawing 7] It is drawing explaining signs that install the hemanalysis equipment of this invention in a centrifugal separator, and centrifugal separation is performed.
[Drawing 8] It is drawing explaining an example of the configuration of the hemanalysis equipment of drawing 5 .
[Drawing 9] They are the conceptual mimetic diagram of the embodiment of the hemanalysis equipment of this invention used in the 2nd example, and drawing explaining the situation after introducing blood into this and performing centrifugal separation.
[Drawing 10] They are the conceptual mimetic diagram of the embodiment of the hemanalysis equipment of this invention used in the 3rd example, and drawing explaining the situation after introducing blood into this and performing centrifugal separation.
[Drawing 11] They are the conceptual mimetic diagram of the embodiment of the hemanalysis equipment of this invention used in the 4th example, and drawing explaining the situation after introducing blood into this and performing centrifugal separation.
[Drawing 12] They are the conceptual mimetic diagram of the embodiment of the hemanalysis equipment of this invention used in the 5th example, and drawing which explains signs that plasma is separated from blood, by the plasma skimming approach of this invention.
[Description of Notations]
101 Substrate
102 Passage
103 Extraction Means

104 Separation Means
105 Analysis Means
106 Migration Means
212 601 Whole blood
301 Bottom Substrate
301A Top substrate
303 Slot Passage
303a Passage upstream section
303b Passage downstream
304, 305, and 801 Service entrance (exhaust port)
306 307 Analysis means
309 Upstream Plasma Component
310 Downstream Plasma Component
311 603 Corpuscle component
501 Corpuscle Reservoir (Corpuscle Fractionation Hold Section)
801 Analysis Means
1101 U Character Passage Lower Part

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

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304, 305, and 801 Service entrance (exhaust port)
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[Translation done.]

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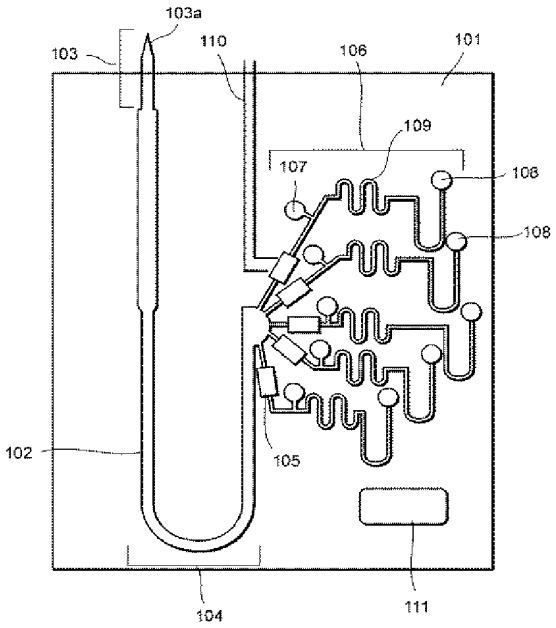
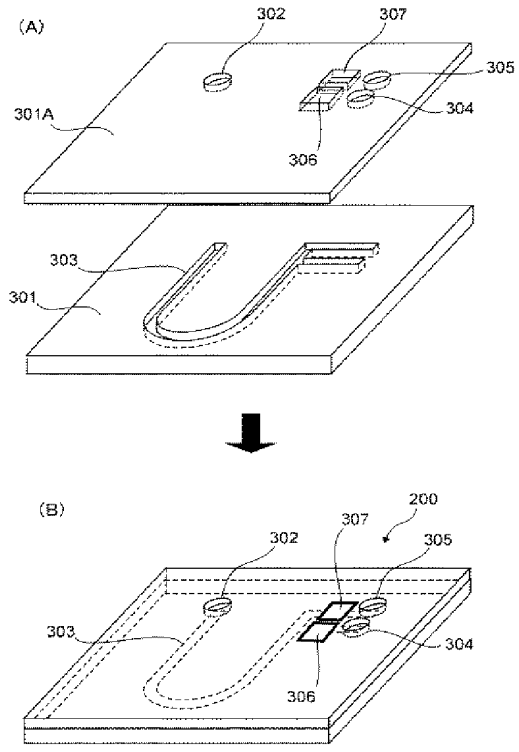
3.In the drawings, any words are not translated.

DRAWINGS

[Drawing 1]



[Drawing 2]



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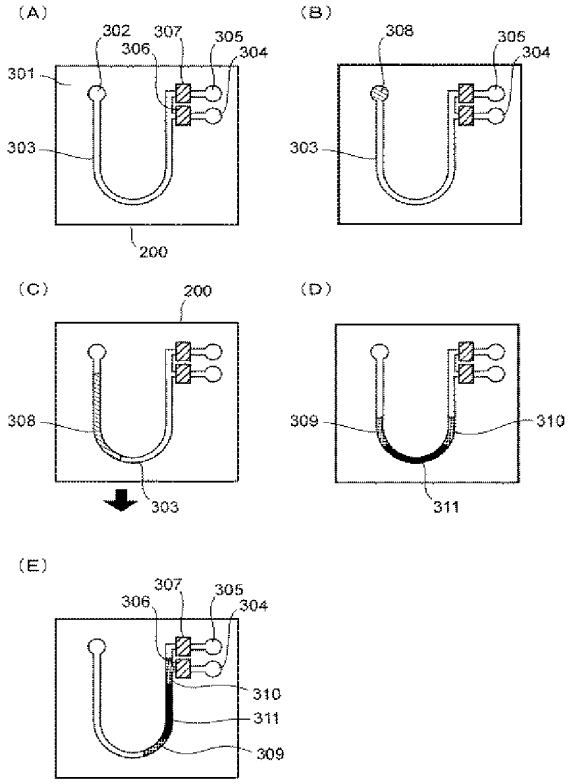

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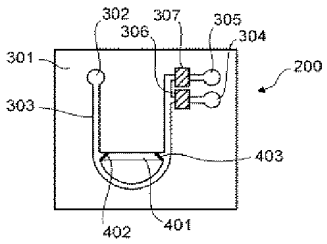

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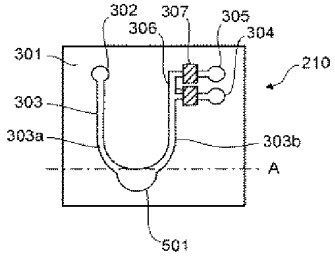

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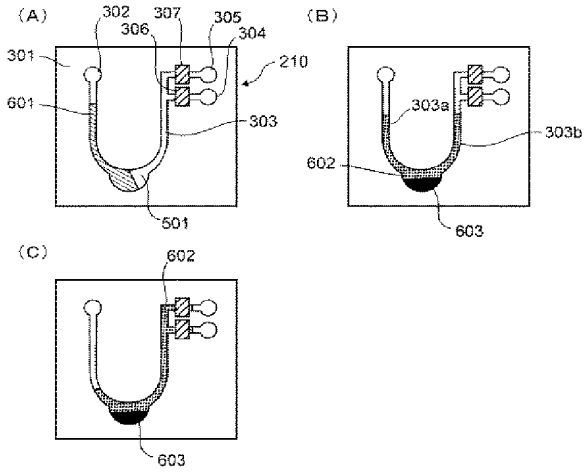

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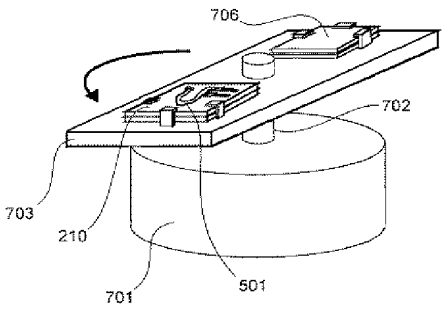

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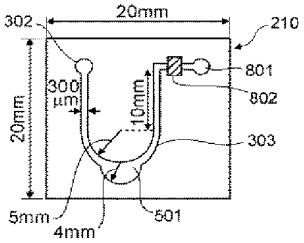

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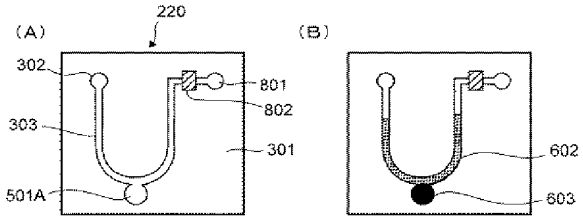

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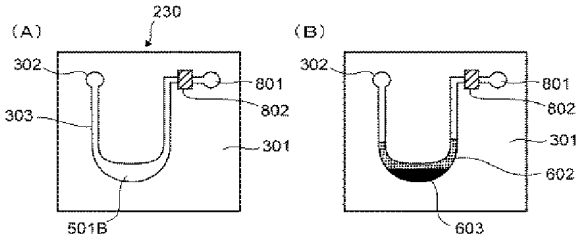

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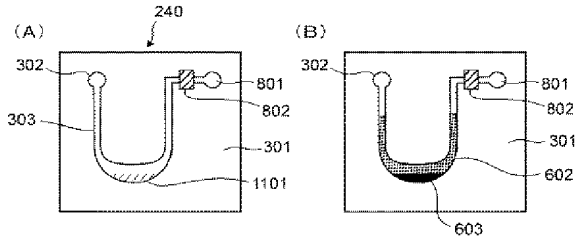
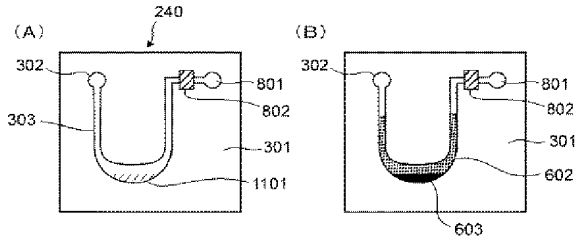


[Drawing 12]



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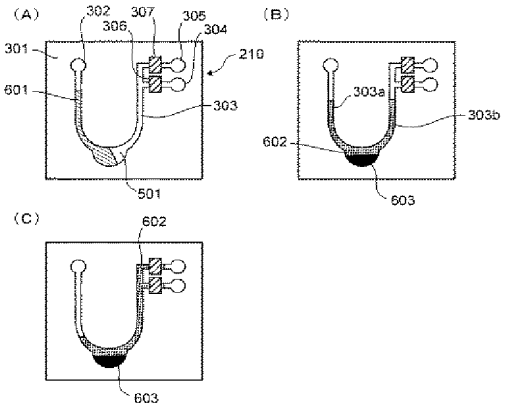
Ｆターム(参考)　2G045 BA08 BB10 CA25 JA07

最終頁に続く

(54)【発明の名称】血液分析装置及び血漿分離方法

(57)【要約】
【課題】遠心操作により流路内で血漿分離を行う自動分析装置において、流路内に導入した全血試料の有効利用を図り、流路長の短縮化、装置の小型化を図る。さらに採血量を減少させることにより被採血者の負担を軽減する。
【解決手段】血液分析装置内の流路に、遠心分離時の遠心方向に血球が沈澱する血球溜めを配置し、そこに遠心分離により血球を集積させ、Ｕ字流路の上流、下流側の血漿分画が血球分画で分断されることなく、連続的に存在するようにする。より少ない全血量で、必要量の血漿を分析手段へと導くことができる。全血試料の有効利用を図れるので、流路長の短縮化、装置の小型化に適する。血球分画で分断されていない血漿は小さな吸引負圧により移動させることができる。血漿引き込みに要するポンプ能力を小さくできることから周辺装置の小型化、コストダウンを図れる。
【選択図】　図６



【特許請求の範囲】
【請求項１】
血液導入口と排出口との間を連通する流路と、この流路の途中に設けられた血漿分離手段とを備える血液分析装置において：
前記流路は、遠心力加圧方向に延伸する前記流路の上流部と遠心力加圧逆方向に延伸する下流部とを備え；
前記血漿分離手段はこれら流路上流部と下流部の間にあって、遠心力加圧方向側に位置して血球分画を沈殿させて収容する血球分画収容部を備え、前記流路の上流部及び下流部は血球分画収容部に接っしつつ血球分画収容部の上部で互いに連通するように構成されていることを特徴とする血液分析装置。
【請求項２】
前記流路の少なくとも一部はＵ字型流路であり、このＵ字型流路最下部が前記血球分画収容部であることを特徴とする請求項１の血液分析装置。
【請求項３】
前記流路の少なくとも一部はＵ字型流路で構成され、このＵ字型流路最下部が前記血球分画収容部であり、
Ｕ字型流路最下部の上部内壁から遠心力加圧方向に位置する前記血球分画収容部の容積が、前記流路に導入される血液中の血球分画量よりも大であることを特徴とする請求項１の血液分析装置。
【請求項４】
前記血漿分離手段と前記排出口の間に、血漿の成分分析を行う分析手段を備えることを特徴とする請求項１の血液分析装置。
【請求項５】
前記血液導入口には、採血針が取り付け可能とされていることを特徴とする請求項１の血液分析装置。
【請求項６】
以下のステップからなる血漿分離方法：
（１）　血液導入口と排出口との間を連通する流路であって、血液導入口から遠心力加圧方向に延伸する上流部と、この下流にあって遠心力加圧逆方向に延伸する下流部とを備える流路と；
流路上流部と下流部の間にあって遠心力加圧方向側に位置して血球成分を沈殿させて収容する血球分画収容部を有し、前記流路の上流部及び下流部は血球分画収容部に接っしつつ血球分画収容部の上部で互いに連通するように構成されている血漿分離手段とを備えるチップ状血液分析装置を用意し；
（２）　前記血液導入口から前記流路に全血試料を導入し；
（３）　血液分析装置を前記血球分画収容部が遠心力加圧方向となるように遠心することにより、血液試料中の血球成分を前記血球分画収容部に沈殿させる一方、前記流路の上流部及び下流部に遠心上清として分離された血漿を、前記血球分画収容部内の血球分画と接しつつ、互いに連続的に存在させる。
【請求項７】
前記血液分析装置は前記血漿分離手段と前記排出口の間に血漿中の成分分析を行う分析手段を備え、
前記ステップ（３）の後に、前記流路の上流部及び下流部に連続的に存在する血漿を前記分析手段に導くことを特徴とする請求項６記載の血漿分離方法。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】
本発明は、石英板や高分子樹脂板などの絶縁材基板に作製した超小型の溝流路によって構成されたチップ状血液分析装置に関する。特に、当該チップ上の溝流路に微量（数μＬ以下）の血液を導入して遠心分離を行い、血球分画と血漿成分に分離した後に血漿成分中の

種々の化学物質濃度を測定する際の、当該血漿成分を有効に活用するための血漿分離方法ならびにこのようなチップ状血液分析装置の溝流路構造に関する。

【０００２】

【従来の技術】

従来の健康診断や疾病状態の診断は、患者から数ｃｃの多量の血液を採取し、その分析に大規模な自動血液分析装置で得た測定値より行われてきた。通常、このような自動分析装置は、病院などの医療機関に設置されており、規模が大きく、また、その操作は専門の資格を有するものに限られるものであった。

【０００３】

しかし、近年、極度に進歩した半導体装置作製に用いられる微細加工技術を応用し、たかだか数ｍｍから数ｃｍ四方のチップ上に種々のセンサなどの分析装置を配置して、そこに被験者の血液などの体液を導き、被験者の健康状態を瞬時に把握することができる新しいデバイスの開発とその実用化の気運が高まってきている。このような安価なデバイスの出現により、来たるべき高齢化社会において老人の日々の健康管理を在宅で可能にすることなどで増加の一途を辿る健康保険給付金の圧縮を図れる。また救急医療の現場においては被験者の感染症（肝炎、後天性免疫不全症など）の有無を本デバイスを用いて迅速に判断できれば適切な対応ができるなど、種々の社会的な効果が期待されるために非常に注目されつつある技術分野である。このように従来の自動分析装置に代わって、血液分析を各家庭で自らの手で実施することを目指した小型簡便な血液分析方法ならびに血液分析装置が開発されている　（例えば、特許文献１参照）　。

【０００４】

【特許文献１】

特開２００１－２５８８６８号公報

【０００５】

図１は、特許文献１に記載されたマイクロモジュール化された血液分析装置の一例を示す。符号１０１は血液分析装置の下側基板であり、下側基板上にエッチングにより形成した微細な溝流路（マイクロキャピラリ）１０２が設けられている。この下側基板１０２の上には、略同一サイズの上側基板（不図示）が張り合わされ、溝流路１０２を外部から密閉している。

【０００６】

流路１０２には、最上流部から最下流部にかけて、血液採取手段１０３，血漿分離手段１０４，分析手段１０５，移動手段１０６が順次設けられている。流路最前部の血液採取手段１０３には、中空の採血針１０３ａが取付けられ、この針１０３ａを体内に刺して基板内への血液の取り入れ口とする。分離手段１０４は、流路１０２の途中を湾曲させたもので例えばＵ字型のマイクロキャピラリからなる。採取した血液をこのＵ字型のマイクロキャピラリに導いた後、本基板を遠心分離器により一定方向に加速度を加えることによって、Ｕ字部最下部に血球成分を沈殿させ、上清として血漿を分離する。分析手段１０５は、血液中のｐＨ値、酸素、二酸化炭素、ナトリウム、カリウム、カルシウム、グルコース、乳酸などの各濃度を測定するためのセンサである。

【０００７】

流路最下流部に位置する移動手段１０６は、マイクロキャピラリ中で血液を電気浸透流により移動させるものであり、電極１０７、１０８と、その間をつなぐ流路部分１０９からなる。この電極間に電圧印加して生じる電気浸透流により流路内に予め満たしておいた緩衝液を流路下流側に移動させ、生じる吸引力によって流路１０２最前部の採取手段１０３から基板内に血液を取り入れる。また、遠心分離により得られた血漿を分析手段１０５に導く。

【０００８】

１１０は分析手段から情報を取出すための出力手段であり、電極などから構成される。１１１は、以上の採取手段、血漿分離手段、分析手段、移動手段、出力手段を必要に応じて制御するための制御手段である。

【０００９】
採取手段１０３より採取された血液は、分離手段１０４にて血漿と血球成分に分離され、この血漿成分を分析手段１０５に導き、そこで血漿中のｐＨ値、酸素、二酸化炭素、ナトリウム、カリウム、カルシウム、グルコース、乳酸などの各濃度を測定する。各手段間の血液の移動は、電気泳動や電気浸透などの現象を用いたものなどポンプ能力を有する移動手段１０６により行う。なお、図１では流路１０２の下流域は５つに分岐し、このそれぞれに分析手段１０５，移動手段１０６が設けられている。
【００１０】
このような血液分析装置の基板には石英などのガラス材料が用いられることが多かったが、装置を大量にまた費用を抑えて製作するのにより適するものとして、樹脂素材が用いられるようになってきている。
【００１１】
【発明が解決しようとする課題】
図１に示した従来の血液分析装置の場合、採取手段１０３により血液を採取し、分離手段１０４にて血漿と血球成分に分離し、この血漿成分を分析手段に導き、血漿中の種々の成分分析を行う。しかしながら分離手段において、血液を遠心分離により血漿と血球成分に分離すると、Ｕ字流路最下部に沈殿した血球分画が流路を塞ぐこととなり、上清である血漿がＵ字流路の上流側１０２ａと下流側１０２ｂに分断される。このため下流側の血漿のみしか分析手段に導くことができず、上流側の血漿成分は利用できないという問題があった。
【００１２】
この様子を図２を用いて簡単に説明する。図２は従来の血液分析装置の作製の様子を示すものである。まず同図（Ａ）のように２枚の基板、例えば樹脂のような材料で構成された下基板３０１および上基板３０１Ａを用意し、一方の下基板３０１上に幅１００ミクロン程度、また深さ１００ミクロン程度の溝流路３０３をモールディングなどの方法により形成する。この溝流路３０３の一部は、図示するようにＵ字型流路が含まれる。上基板３０１Ａ上には、被検査血液を導入するための入力側貫通穴３０２、血液を流路へと引き込むために外部ポンプを接続するための出力側貫通穴３０４，３０５および血漿中のそれぞれ異なる項目を検出する分析手段３０６，３０７が構成されている。両基板３０１，３０１Ａ２を互いに熱圧着、接着剤、接着テープなどにより接合して血液分析装置２００を作製する（同図（Ｂ））。
【００１３】
図３はこうして作製された血液分析装置の平面模式図であり、ヒト全血を血液分析装置の流路に導入して遠心分離する様子を示す。図３（Ａ）に示す血液分析装置の入力側貫通穴（血液導入口）３０２に１μＬ程度の血液をたらし（同図（Ｂ））、出力側貫通穴（排出口）３０４、３０５からポンプで流路３０３へと全血３０８を導く（同図（Ｃ））。次にＵ字流路方向（同図（Ｃ）中の矢印方向）に力が作用するように血液分析装置２００を回転させ遠心分離を行う。すると同図（Ｄ）に示すようにＵ字流路３０３の両側に血漿分画３０９、３１０とＵ字流路下部に血球分画３１１とに全血が分離される。その後に出力側貫通穴３０４、３０５にポンプ等を接続して、下流側血漿分画３１０を分析手段３０６、３０７へと導いていき（同図（Ｅ））、そこでそれぞれの被検査化学物質の検出・濃度測定を行う。
【００１４】
しかしながらこのようなＵ字流路の場合、同図（Ｄ）で示される上流側血漿分画３０９は、血球分画３１１に流路を塞がれ、分析手段に導いて使用することができない。これは検査に必要な血液量を不必要に増加させていることを意味し、もしこのような上流側の血漿分画も分析手段へと導き用いることができれば、検査に必要な血液量は単純に約半分にまで減少することができる。このことは、流路の全長を短縮し、ひいては血液分析装置全体のさらなる小型化を可能にする。
【００１５】

また図１～３の従来血液分析装置では、図３（Ｅ）に示すように全血の遠心分離後に下流側血漿成分３１０を分析手段３０６、３０７へと導く際には、血球分画３１１と上流側血漿成分３０９も同時に移動させなければならない。このとき血球分画３１１は流路３０３の内壁にへばりついているので、ポンプ等でこれらを移動させるためには、遠心前に全血を流路に引き込むときよりも大きな吸引力ポンプ力が必要されるという問題があった。

【００１６】

【課題を解決しようとする課題】

上記のような課題を解決する手段として、図４に示すようにＵ字流路の上流側と下流側との間に新たにバイパス流路４０１を設ければ、遠心分離後、上流側血漿を下流側へと導くことができる。しかし、そのためには遠心分離が終了するまでこのバイパス流路を閉めておく必要があり、このバイパス流路４０１の出入り口に新たに弁４０２、４０３を設置しなければならず、これの制御を含めると大がかりな装置となってしまい現実的ではない。

【００１７】

そこで本発明の発明者らは遠心分離後の血球成分が流路の壁にへばりついていることに注目して、これを逆に利用することで若干の流路形状の改良のみで従来装置の課題を克服することを試みた。すなわち、遠心分離により血球成分と血漿成分が分離したときの血球成分が溜まる部分の流路を他のそれよりも太くし、そこに血球成分を溜め、また上流側と下流側の血漿成分はその溜め部分の血球の溜まっていない部分を介して連続的に血漿でつながっているようにする。このようにした後にポンプ等で分析手段へと血漿を引き込めば、上流側と下流側の血漿は連続的につながっているので、それほど大きなポンプ力を必要とせず、かつ分離したすべての血漿成分を分析手段へと導くことができる。

【００１８】

すなわち、本発明は、遠心操作により流路内で血漿分離を行う自動分析装置であって、流路内に導入した全血試料の有効利用を図り、流路長の短縮化、装置の小型化に適し、さらに採血量を減少させることにより被採血者の負担を軽減することができる血液分析装置を提供することを第１の目的とする。

【００１９】

また本発明は、遠心操作により流路内で血漿分離を行う自動分析装置を使用する際に、流路内に導入した全血試料の有効利用を図ることができる血漿分離方法を提供することを目的とする。

【００２０】

【発明の構成】

本発明によれば、第１の目的は、血液導入口と排出口との間を連通する流路と、この流路の途中に設けられた血漿分離手段とを備える血液分析装置において：前記流路は、遠心力加圧方向に延伸する前記流路の上流部と遠心力加圧逆方向に延伸する下流部とを備え；前記血漿分離手段はこれら流路上流部と下流部の間にあって、遠心力加圧方向側に位置して血球分画を沈殿させて収容する血球分画収容部を備え、前記流路の上流部及び下流部は血球分画収容部に接っしつつ血球分画収容部の上部で互いに連通するように構成されていることを特徴とする血液分析装置、により達成される。

【００２１】

例えば、流路の一部をＵ字型流路とすれば、このＵ字型流路最下部（遠心力のＧがかかる部分）を血球分画収容部とすることができる。この血球分画収容部は、Ｕ字型流路の最下部から下方（遠心Ｇ加重方向）に突出した空間であればよくＵ字型流路最下部の上部内壁から遠心力加圧方向に位置する血球分画収容部の容積が、前記流路に導入される血液中の血球分画量よりも大であれば、血球分画収容部の上部は上流部・下流部の上清血漿を連通することができる。

【００２２】

血漿分離手段と排出口の間に、血漿の成分分析を行う分析手段を設けてもよい。また血液導入口に採血針を取り付け可能とすれば、採血針から採血した全血を直接流路内に導入することができる。

【００２３】
本発明の第２の目的は、以下のステップからなる血漿分離方法：
（１）　血液導入口と排出口との間を連通する流路であって、血液導入口から遠心力加圧方向に延伸する上流部と、この下流にあって遠心力加圧逆方向に延伸する下流部とを備える流路と；
流路上流部と下流部の間にあって遠心力加圧方向側に位置して血球成分を沈殿させて収容する血球分画収容部を有し、前記流路の上流部及び下流部は血球分画収容部に接っしつつ血球分画収容部の上部で互いに連通するように構成されている血漿分離手段とを備えるチップ状血液分析装置を用意し；
（２）　前記血液導入口から前記流路に全血試料を導入し；
（３）　血液分析装置を前記血球分画収容部が遠心力加圧方向となるように遠心することにより、血液試料中の血球成分を前記血球分画収容部に沈殿させる一方、前記流路の上流部及び下流部に遠心上清として分離された血漿を、前記血球分画収容部内の血球分画と接しつつ、互いに連続的に存在させる、によって達成することができる。
【００２４】
血液分析装置の血漿分離手段と排出口の間に血漿中の成分分析を行う分析手段を備えている場合には、ステップ（３）の後に、流路の上流部及び下流部に連続的に存在する血漿を分析手段に導くことができる。
【００２５】
【実施態様】
図５は本発明に基づく流路を有する血液分析装置の一実施態様を示す。本血液分析装置２１０は基本的には図３に示した装置２００とほとんど同じ構成であるが、Ｕ字流路最下部の遠心分離時に最も重力加速度が印加されるあたりの流路３０３をくびれさせて、広くしてある血球溜め（血球分画収容部）５０１がある点が異なる。同一構成部分には同一符号を付してるので説明を繰り返さない。
【００２６】
この血液分析装置の動作の様子を以下に説明する。図６（Ａ）に示すように血液分析装置に全血を導入した後、図７に示すような遠心分離装置に当該血液分析装置２１０をセットして全血の遠心分離を行う。このとき回転の遠心方向に血液分析装置上の血球溜め５０１があるように血液分析装置２１０を設置し、この血球溜め５０１に遠心により血球分画が沈澱する。なお、７０１はモーター、７０２はモータシャフト、７０３はチップ支持板、７０６はバランサチップである。
【００２７】
遠心操作後の血液分析装置２１０の流路内の様子を図６（Ｂ）に示す。血球溜め５０１下部には血球分画６０３が遠沈し、またその上部の流路３０３には血漿成分６０２が上清として分離される。このとき、従来の血液分析装置の場合（図３参照）とは異なり、血漿分画がＵ字流路内で上流部３０３ａから下流部３０３ｂにかけて血球分画６０３に分断されることなく連続的に存在することが重要である。
【００２８】
このためには、図５に図示するように流路３０３の最下部での内壁上端位置Ａから下方に位置する血球溜め（血球成分収容部）５０１の容量が、流路３０３に導入された全血中の血球成分量より大となるようにする。ヒトのヘマクリット値は通常５０％以下であるから、血球溜め（血球成分収容部）５０１の容量は、採血量の１／２以上とするのが好ましい。血球溜めの容量は、Ｕ字流路の流路長・断面積も考慮して決定することができる。なお、ヘマクリット値が高く、血球溜め上端Ａを越えて血球が分画されるような場合には、採血量を減らすことにより対処できる。
【００２９】
遠心分離後、流路３０３最下流部に配置されている引き込み口（排出口）３０４、３０５に外部吸引ポンプを接続して、血漿分画６０２を分析手段３０６、３０７へと引き込んでいく。Ｕ字流路の下流部３０３ｂと上流部３０３ａの血漿分画６０２が血球分画６０３で

遮られていないので、分離した血漿分画をすべて分析手段３０６，３０７へと導くことができる（図６（Ｃ））。

【００３０】

血球分画は血球溜め５０１下部の内壁に遠心加重により固着している。従って、血漿分画を分析手段に吸引移動する際に、血球分画が移動することはない。血漿の吸引移動は、液性成分である血漿分画の移動のみで行うことができ、血球分画も併せて移動しなければならなかった従来の場合のように大きなポンプ力が必要とはならない。

【００３１】

このように血液分析装置内の流路に、遠心分離時の遠心方向に血球が沈澱する血球溜めを配置し、そこに遠心分離により血球を集積させ、Ｕ字流路の上流、下流側の血漿分画が血球分画で分断されることなく、連続的に存在するようにすることができれば、分離したすべての血漿分画を分析手段へと引き込むことができ、かつそのときの引き込みに必要となるポンプ力は低くてすむ。このような血球溜めの寸法は、Ｕ字流路寸法と遠心分離を行う全血量からその４０から５０％（体積）が血球成分であることを考慮することで決定することができる。

【００３２】

なおこの実施態様では、外部ポンプを用いて血液の導入、血漿分画の吸引を行ったが、図１の従来装置のように電気浸透流を利用した移動手段を分析手段と引き込み口（排出口）との間に設けてもよい。この場合排出口３０４，３０５は流路内に充填されていた緩衝液の排出口となる。

【００３３】

【第１実施例】

図５に示した血液分析装置を作製し、血液試料を血液分析装置内に導入して遠心分離を行い、その後血漿分画の吸引を行った。ただし、簡単のため血液分析装置内の分析手段は１つにした（図８参照）。血液分析装置は０．５ｍｍ厚の２枚のポリエチレンテレフタレート（ＰＥＴ）基板を用意し、一方の基板上に、モールディングによって流路３０３を形成し、もう一方の基板上には、血液導入口３０２、血液引き込み口（排出口）８０１、およびカーボンペーストで形成した電極上に水素イオン感応膜を塗布したものを分析手段８０２として作製、配置した。図８に、血液分析装置２１０とその上に形成した流路３０３の寸法の概略を示す。なお流路の深さはすべて１００μｍである。

【００３４】

この血液分析装置２１０の血液導入口３０２から１μＬのヒトの全血を導入した。血液の導入には排出口８０１に取り付けた電磁ポンプの吸引力を用いた。そのときの吸引負圧は、大気圧から－７ｋＰａであった。血液導入後に、図７に示したような遠心機により血液分析装置を遠心した（１００００ｒｐｍ、２２５０Ｇ，１分）。遠心後の血液分析装置流路内は図６（Ｂ）に示すように血球溜め５０１下部に血球分画６０３が沈澱し、また血漿成分はその血球溜め上部と上流および下流のＵ字流路内に血球成分によって血漿成分同士が絶縁されることなく連続的に存在するように分離された。この後に分析手段下流部にある引き込み口３０４，３０５に電磁ポンプを接続し、当該血漿成分を分析手段に導いた。このとき血球成分は移動せず、血漿成分のみ移動した。ここで血漿中の水素イオン濃度を調べたところ、ｐＨ　７．４を示し、健常者の血漿ｐＨ値とほぼ同じであった。また血漿引き込み圧は、全血引き込み圧と同じ大気圧より－７ｋＰａで問題なく引き込むことができた。

【００３５】

また、図８の血液分析装置を改造し、血液導入口３０２に外径１００μｍ、内径５０μｍの中空の採血針を取り付けた場合についても同様な試験を行った。まず血液分析装置上の採血針をヒトの前腕部に穿刺し、約１μＬの血液を採取して当該血液分析装置上に導く。その後は上で述べた手順と同様に遠心分離により血漿と血球分画に分離し、血漿のみを分析手段へと導いた。ここで血漿の水素イオン濃度を調べたところ、上の場合と同様にｐＨ　７．４を示し、健常者の血漿の値とほぼ同じであった。

【００３６】
【比較例】
図３に示した従来の血液分析装置を用いて全血の引き込み、遠心分離による血漿および血球成分分離、および血漿成分の分析手段への引き込みを同様に行った。このときのＵ字流路の幅は５００μｍ、深さは１００μｍとした。またこの場合も分析手段は一つとし、カーボンペーストで形成した電極上に水素イオン感応膜を塗布したものを用いた。このような血液分析装置の血液導入口２０４から１μＬのヒトの全血を導入した。血液の導入には排出口２０５に取り付けた電磁ポンプを用い、そのときの吸引負圧は、大気圧から－７ｋＰａであった。
【００３７】
図３（Ｃ）に示すが如くに血液分析装置内に血液を導入した後に、図７に示したような遠心分離器に血液分析装置を設置し、遠心分離を行った（１００００　ｒｐｍ、２２５０Ｇ，１分）。遠心により、図３（Ｄ）に示すように単Ｕ字管内で血漿成分３０９，３１０と血球成分３１１が分離された。このときの特徴は図５に示したような流路途中に血球溜めを有する血液分析装置の場合とは異なり、単Ｕ字流路の上流側と下流側の血漿成分３０９，３１０が血球分画３１１により絶縁された。
【００３８】
この後に分析手段下流部にある引き込み口３０４，３０５に電磁ポンプを接続し、単Ｕ字流路の下流側の血漿成分３１０を分析手段３０６，３０７へと導いた。このときの吸引負圧を第１実施例と同じ－７ｋＰａとしても血漿を引き込むことはできなかった。吸引負圧を徐々に上昇させていき、大気圧から－３８ｋＰａに達したところで流路下流側の血漿３１０が移動しはじめた。またこの移動に伴い、Ｕ字流路下部の血球成分および上流側血漿成分も同時に移動した。第１実施例の場合の血漿引き込み圧と比較して、この比較例ではより大きな血漿引き込み圧が必要であった。これにより本発明の効果がより鮮明となった。
【００３９】
このような過大な引き込み圧が必要とされるのは遠心分離により流路の壁に付着している血球分画を成分と共に血漿成分を引き込まなくてはならないためであると考えられる。さらに図３のような単Ｕ字血液分析装置の場合、過大な引き込み圧で血漿を引き込んでも、実際に分析手段へと引き込める血漿は下流側に分離された血漿成分のみで、血球分画で塞がれた上流側の血漿は分析手段へ引き込むことができない。従来の血液分析装置においては分離された血漿の約半分しか分析手段へと導けない。これに対し、図５に示した本発明の血球溜めを有する血液分析装置の場合には、分離したすべての血漿を分析手段へと導くことができる。従って、同量の血漿を分析手段へと導く場合、本発明の場合の方が従来の場合よりも血液分析装置内に導入する血液量が約半分でよいという利点がある。
【００４０】
【第２実施例】
図９（Ａ）に示すような血球溜め５０１Ａを有する血液分析装置２２０を作製し、血液を当該血液分析装置内に導入して遠心分離を行い、その後血漿分画６０２の引き込みを行った。なお、当該血液分析装置および流路形状の寸法は、図８に示した寸法にほぼ類似している。この血液分析装置のと、図８の血液分析装置との違いは、図９（Ｂ）に示したように血液を血液分析装置上に導入して遠心分離を行なったときに、分離した血漿６０２と血球分画６０３の界面の面積が図８で示した血液分析装置の場合と比して小さくなっているところである。これにより、血漿吸引時に血球分画に印加される引き込み力が小さくなり、血球分画表面が撹乱されて血漿に混入するのを防止することができ、血漿のほぼ全てを分析手段へと移動させることを確実にする。
【００４１】
実際に血液導入口から１μＬのヒトの全血を導入して遠心分離を行なったところ、図９（Ｂ）に示すように血球と血漿成分が分離された。またその後に引き込み口８０１にポンプを接続し、大気圧から－７ｋＰａの圧力で引いたところ血漿成分６０２のみを分析手段８

０２側へと引き込むことができた。このとき血球溜めにある血球成分は移動せず、そのまま血球溜めに留まっていた。

【００４２】

【第３実施例】

図１０（Ａ）に示すようにＵ字流路３０３下部の流路幅を広くしてここを血球溜め５０１Ｂとした血液分析装置２３０を作製し、第１，２実施例と同様に血液の導入、血漿血球成分分離および血漿成分引き込みを試みた。その結果、血液導入後の遠心分離により、図１０（Ｂ）に示す如く血漿６０２と血球分画６０３が分離され、また血球分画６０３を撹乱することなく血漿分画６０２のみを引き込み、分析手段８０２へと導くことができた。本実施例より遠心により血漿と血球分画に分離したときに、血漿分画が血球分画によって分断されずに連続的に存在していることが特に重要であることが分かる。これは第１，２実施例で示した血球溜めを流路途中に有する血液分析装置においても同様である。

【００４３】

【第４実施例】

Ｕ字流路３０３下部の流路幅と流路深さを大きくした血液分析装置を作製した。すなわち、図１１（Ａ）に示すＵ字流路３０３下部の斜線部１１０１の深さを、他の流路部分の深さ１００μｍより深い３００μｍとした血液分析装置２４０を作製した。第３実施例と同様に血液の導入、血漿分離および血漿成分引き込みを試みた。遠心分離により、図１１（Ｂ）に示す如く血漿６０２と血球分画６０３に分離され、また血球分画６０３は移動させることなく血漿分画６０２のみを引き込み、分析手段８０２へと導くことができた。

【００４４】

ここで注目すべきことは、図１１（Ａ）のＵ字流路下部１１０１の深さが深く、この部分の容積は図１０の血液分析装置のそれに比して３倍大きくなるためにここに血球成分が集積する。したがって第３実施例の場合と同量の血液を血液分析装置上に導入して遠心分離をした場合、図１１上面から見た血球分画６０３のの構成面積が、血漿成分が占める面積に対する比率は、図１０の場合よりも小さくなる。したがってＵ字流路下部における血漿成分の構成する幅が図１０（Ｂ）に比して広くなることから、この血球および血漿成分分離後の血漿成分引き込みにおいては、より低い引き込み圧力で当該血漿成分を引き込むことができる。

【００４５】

【第５実施例】

図１２（Ａ）に示すような単Ｕ字流路血液分析装置を作製し、これまでの実施例と同様に血液の導入、血漿血球成分分離および血漿成分引き込みを試みた。このとき流路の幅や深さは導入する血液の量（必要となる血漿の量）から決定した。すなわち、遠心分離後に血漿成分が流路上で血球分画で分断されずに図１２（Ｂ）のように連続的に存在するようにした。実際に図１２（Ｃ）に示すような寸法で流路深さ１００μｍの単Ｕ字流路３０３を有する血液分析装置２５０を作製して、この血液分析装置上に０．１μＬの血液を導入し、遠心分離を行った。その結果、図１２（Ｂ）に示すように血漿分画６０２と血球分画６０３とに分離され、その後分離したすべての血漿分画のみを分析手段８０２に導くことができた。このように必要となる血漿量から導入する血液量を見積もり、遠心分離後に血漿成分が流路上で血球分画で分断されないように流路の設計を行えば、必ずしも図５に示したような血球溜めは必要ではない。流路設計に基づいて設けられたＵ字流路最下部が血球溜め（血球分画収容部）を構成することになる。

【００４６】

【発明の効果】

以上のように、本発明の血液分析装置は、装置内に血液を導入する流路の一部に、遠心力加圧方向の位置して血球分画を集める血球分画収容部を設け、収容部の上流側及び下流側の流路が連通するようにした。これにより、遠心分離後の血球分画に分断されることなく、流路上流部と下流部の血漿分画が連続して存在することができる。従って、従来の流路構成の場合に比して、より少ない全血量、単純には半分の量の血液試料で、必要量の血漿

を分析手段へと導くことができる。全血試料の有効利用を図れるので、流路長の短縮化、装置の小型化に適する。さらに採血量を減少させることにより被採血者の負担を軽減することができる

【００４７】

また、分離された血漿分画は血球分画で分断されないので、より小さな吸引負圧により移動させることができる。血漿引き込みに要するポンプ能力を小さくできることから周辺装置の小型化、コストダウンを図れる。

【図面の簡単な説明】

【図１】従来のチップ状血液分析装置の説明図である。

【図２】チップ状血液分析装置作製の工程の説明図である。

【図３】血液分析装置上に全血を導入し、遠心分離により血漿と血球分画に成分に分離する様子を示す図である。

【図４】従来の血液分析装置の構成の変更例を示す図である。

【図５】本発明の血液分析装置の一実施態様の概念模式図である。

【図６】図５の血液分析装置に血液を導入して、血漿と血球分画とに分離し、その後に血漿分画を分析手段へ導く各工程を説明する図である。

【図７】遠心分離装置に本発明の血液分析装置を設置し、遠心分離を行っている様子を説明する図である。

【図８】図５の血液分析装置の構成の一例を説明する図である。

【図９】第２実施例で使用した本発明の血液分析装置の実施態様の概念模式図と、これに血液を導入して遠心分離を行った後の様子を説明する図である。

【図１０】第３実施例で使用した本発明の血液分析装置の実施態様の概念模式図と、これに血液を導入して遠心分離を行った後の様子を説明する図である。

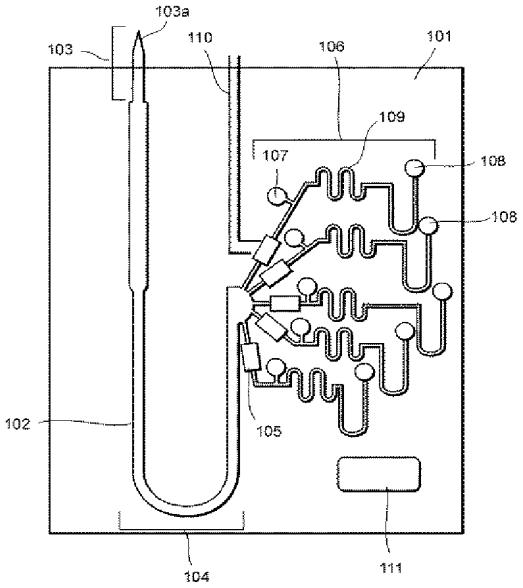
【図１１】第４実施例で使用した本発明の血液分析装置の実施態様の概念模式図と、これに血液を導入して遠心分離を行った後の様子を説明する図である。

【図１２】第５実施例で使用した本発明の血液分析装置の実施態様の概念模式図と、本発明の血漿分離方法により、血液から血漿を分離する様子を説明する図である。

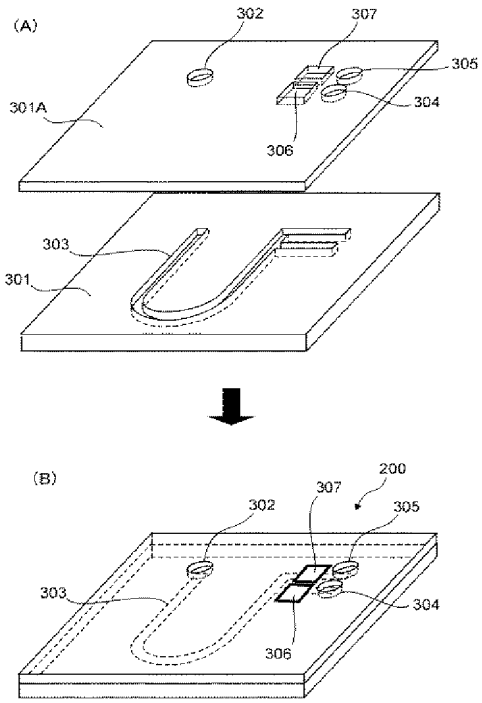
【符号の説明】

１０１　基板
１０２　流路
１０３　採取手段
１０４　分離手段
１０５　分析手段
１０６　移動手段
２１２、６０１　全血
３０１　下側基板
３０１Ａ　上側基板
３０３　溝流路
３０３ａ　流路上流部
３０３ｂ　流路下流部
３０４、３０５、８０１　引き込み口（排出口）
３０６、３０７　分析手段
３０９　上流側血漿成分
３１０　下流側血漿成分
３１１、６０３　血球成分
５０１　血球溜め（血球分画収容部）
８０１　分析手段
１１０１　Ｕ字流路下部

【図１】


103a
103
110
106
101
109
107
108
108
102
105
104
111

【図２】


(A)
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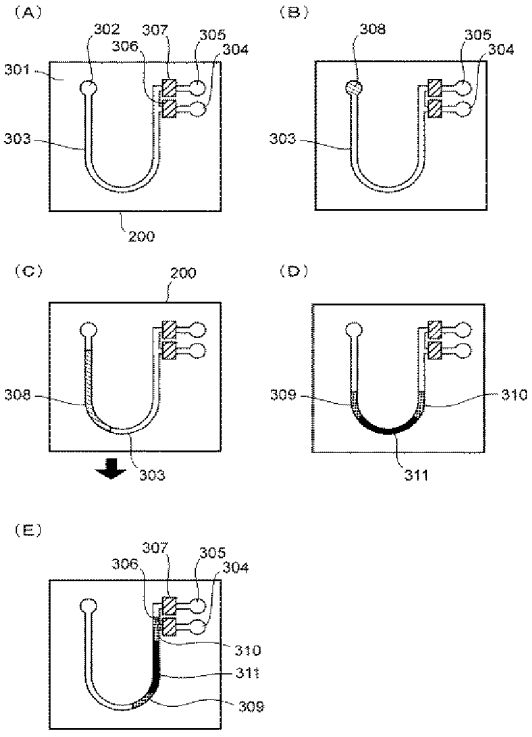
307
305
301A
304
306
303
301
(B)
200
307
302
305
303
304
306

【図３】


(A)
302
307
306
305
304
301
303
200
(B)
308
305
304
303
(C)
200
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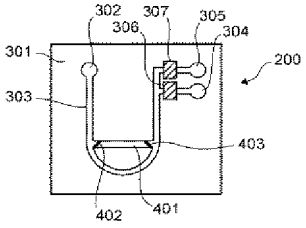
303
(D)
309
310
311
(E)
307
306
305
304
310
311
309

【図４】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301
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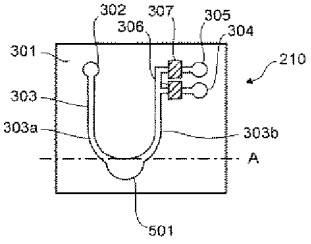
303
403
402
401

【図５】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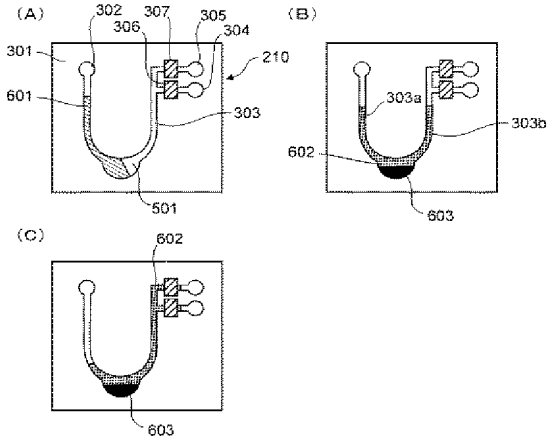
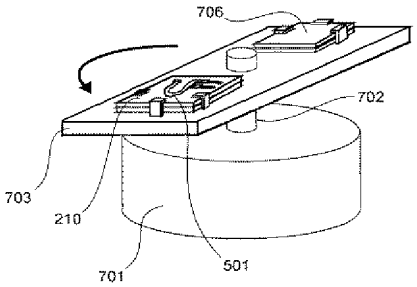
304
301
210
303
303a
303b
A
501

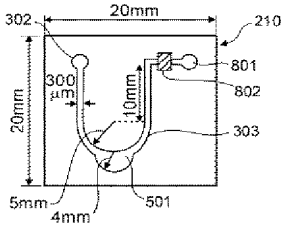
【図６】



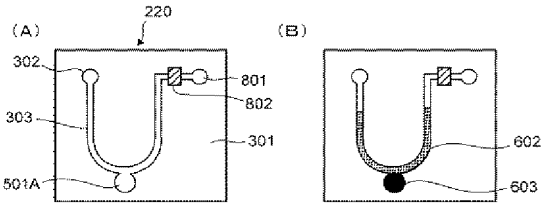
【図７】



【図８】



【図９】



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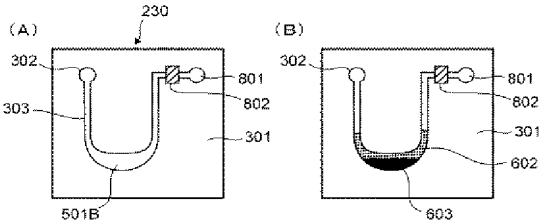

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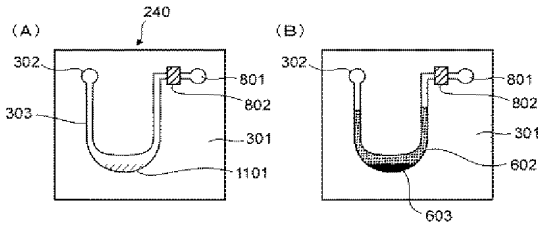

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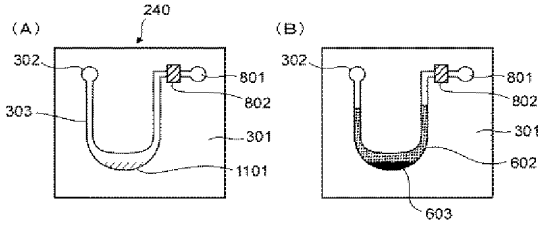

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Fターム(参考) 2G052 AA30 AD29 AD46 CA03 CA04 CA08 ED16 ED17 JA01 JA11
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